NTP Study Nomination: Pentaethylenehexamine

Nomination

Pentaethylenehexamine (PEHA) was nominated by the NCI with moderate priority for *in vitro* toxicity studies to determine whether the corrosive nature of this compound would prevent humane testing in animal studies. If testing is feasible, the NCI recommends the following: (1) mammalian genotoxicity studies, (2) toxicological characterization including chronic toxicity and carcinogenicity studies, and (3) developmental toxicity studies. The rationale for this nomination is based on high production volume, potential worker exposures, lack of adequate toxicological data, and positive mutagenicity data.

Background

PEHA is sold as a technical product or at ~ 40% in a distillation cut with higher polyamine products. It is primarily produced by treating ethylene dichloride with excess ammonia under high pressure at moderate temperatures or as a product with other ethyleneamines that are produced by treating ethylene oxide with monoethanolamine. The production volume reported in the U.S. EPA Inventory Update Rule database for 2002 was >1 to 10 million pounds (> 450 to 4500 metric tons). PEHA is a chemical intermediate used in a number of industrial applications including production of ion-exchange resins, do-it-yourself floor coatings, hardeners for both industrial and consumer epoxy resins, chemicals that are mixed with asphalt to pave roads, and corrosion inhibitors in lubricating oil, fuels, and metal paint primers. Workers and consumers may be exposed to PEHA during the production processes or use of PEHA-containing consumer products. Release into waste streams is also of concern because PEHA biodegrades slowly and is extremely toxic to aquatic organisms. PEHA is described as a potential skin sensitizer and corrosive that may burn the eyes, skin, gastrointestinal tract, and respiratory tract, causing severe and permanent damage. Inhalation damage may progress to lung and laryngeal edema, chemical pneumonitis, and death. The rat oral LD_{50} has been reported as 1,600 mg/kg and 4,130 mg/kg. PEHA was corrosive to rabbit eyes and moderately irritating to rabbit skin. It was positive in *Salmonella* mutagenicity tests with metabolic activation and equivocal in the *Drosophila melanogaster* sex-linked-recessive lethal assay at 25,000 ppm. Plausible mechanisms for metabolism include oxidative deamination by polyamine oxidase and oxidative *N*-dealkylation. PEHA has not been tested in subchronic, chronic, or carcinogenesis bioassays, but DEREK, a program for predicting toxicity, concludes it is plausible that PEHA will be carcinogenic to rodents. Two lower congeners, triethylenetetramine and tetraethylenepentamine, have been studied more extensively in mammalian genotoxicity and carcinogenesis bioassays. Neither induced tumors in C3HeJ mice (single dose, dermal treatment, three times per week), micronuclei in mice *in vivo*, nor gene mutation in CHO cells. Both were equivocal in the *Drosophila melanogaster* sex-linked-recessive lethal assay and produced sister chromatid exchanges in CHO cells and unscheduled DNA synthesis in rat hepatocytes. Both analogs were positive in *Salmonella typhimurium* strains TA98 and TA100 with and without metabolic activation while only triethylenetetramine was mutagenic in *Escherichia coli* without metabolic activation.

Study Recommendations

No studies of PEHA are recommended at this time due to the irritant and corrosive nature of this compound. Though there are no occupational exposure guidelines or hazardous waste regulations for PEHA, there is information in the literature documenting skin and eye irritancy and potential skin sensitization. Additional *in vitro* studies would add little to this body of knowledge. Irritancy and corrosivity would likely preclude humane *in vivo* studies at sufficiently challenging doses though studies may be feasible at lower exposure levels.